Residual Symptoms in Depression: Can Treatment Be Symptom-Specific?

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Background: Most patients with depression continue to have symptoms after treatment. It is well documented that these "residual" symptoms are common and are associated with increases in suboptimal long-term outcomes such as relapse and disability. While it is clear that residual symptoms, as a group, contribute to poor outcomes, individual residual symptoms have received relatively little attention. To some extent, this lack of attention reflects an uncertainty in the field about the relationship of the syndrome of depression to the symptoms by which the syndrome is defined.

Method: Recognizing that for clinicians and patients symptom relief is the goal of treatment, this article reviews the evidence that a symptomatic approach to individual residual symptoms is both feasible and useful. Evidence was gathered through a MEDLINE review of articles published in English from 1966 to 2002. Multiple keywords relating to symptoms, depression, and treatment were used.

Results: Many of the agents that psychiatrists use for augmentation of depression treatment, such as psychostimulants and alerting agents, atypical antipsychotics and mood stabilizers, and buspirone and benzodiazepines, have specific symptomatic effects, which raises the question of whether we are augmenting the core antidepressant effect or providing symptomatic relief. Fatigue, anxiety, sexual dysfunction, and sleep disturbances are all symptoms that are commonly leftover after treatment of depression. Some data indicate that treatment of these residual symptoms is efficacious and may affect the long-term outcome of depression.

Discussion: This discussion of the treatment of residual depressive symptoms raises a variety of research questions that should be addressed. Also implicit in this discussion are theoretical questions on the relationship between symptoms and syndrome.

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That many, if not most, depressed patients continue to have symptoms after treatment is common clinical wisdom. It is now apparent that residual symptoms are common, not only in patients with partial response, but also in patients who meet criteria for response or remission.[1,2] Thus, despite the progress that has been made in the treatment of depression, this suboptimal outcome is present in the majority of treated patients.[3,4]

Residual symptoms are associated with a variety of poor outcomes, including relapse, work impairment, and emotional distress.[5–10] Even with relatively mild residual symptomatology, disability appears to be associated in a linear fashion with symptom severity, so that as symptom severity increases, so does disability.[8,10]

Despite the prevalence and importance of residual symptoms, most research has focused on patients with a lack of response to treatment (treatment-resistant depression). This research generally involves strategies directed at the syndromic depression per se, such as dose adjustment, switching, and augmentation.[11,12] This conceptual focus on the syndrome of depression, at the expense of the symptomatic, has led to a paucity of literature on the management of residual or "leftover" symptoms. The fact that many of the augmenting agents psychiatrists are using, such as psychostimulants and alerting agents, atypical antipsychotics and mood stabilizers, and buspirone and benzodiazepines, have specific symptomatic effects justifies the question of whether we are actually augmenting the core

antidepressant effect or providing symptomatic relief. Recognizing that for most clinicians and patients the goal of treatment is symptom relief, it is surprising that there is little literature on a symptomatic approach to residual symptoms, that is, targeting of individual symptoms that remain after successful or partially successful treatment of depression.

To some extent, this lack of literature reflects an uncertainty in the field regarding the relationship between the syndrome of depression and the symptoms that define the syndrome, as well as our understanding of the term "residual." Residual symptoms are generally thought of as core depressive symptoms that have not resolved with treatment, but symptoms remaining after treatment may have a variety of etiologies. Some symptoms that appear to be "residual" may be independent comorbidities secondary to a medical disorder. A "residual" symptom may also be treatment emergent, as in fatigue secondary to a side effect of a medication. Most studies that discuss residual symptoms have not attempted to tease apart these various relationships of symptoms to syndrome.

It is also unclear at what point residual symptoms are sufficiently mild enough to exert no practical impact in important outcomes such as quality of life. A study by Fava et al.[13] suggests that in normal controls the mean Hamilton Rating Scale for Depression (HAM-D) score is 6. Thus, at some point it may be unreasonable or infeasible to attempt to make patients completely asymptomatic. The issue remains to be elucidated, as it may also be that, in depression, it is possible and desirable to struggle for a completely or nearly asymptomatic state.

Many symptoms that remain after treatment, such as fatigue, sleep difficulties, anxiety, and sexual dysfunction, are potentially treatable, and resolution of these symptoms may lead to more successful long-term outcomes. The purpose of this article is to review the data on the prevalence and importance of residual symptoms and to review the available data on treatment of these symptoms. In addition, we suggest that research is needed on individual symptoms leftover after treatment and that further study may lead to a more practical, symptom-based approach to these problems. We also briefly discuss the relationship of residual symptoms to the syndrome of depression. Evidence was gathered through a MEDLINE search of articles published in English from 1966 to 2002. Multiple keywords relating to symptoms, depression, and treatment were used.

PREVALENCE OF INDIVIDUAL RESIDUAL SYMPTOMS

A variety of studies, both acute and long-term, with different methodologies, have demonstrated that most patients continue to experience symptoms after treatment with psychotherapy or antidepressants.[1,2,5–7,10,14–21] While outcomes are generally now reported in terms of response, remission, and partial response,[22–24] residual symptoms appear to be common across all of these categories. However, individual symptoms are generally not reported in clinical trials, with most studies describing the presence or absence of residual symptoms as a group. Furthermore, these studies generally do not attempt to identify those residual symptoms resulting from medication side effects and independent medical comorbidities.

Identifying the specific patterns of residual symptoms may have direct effects on future treatment options. Specifically, patients with suboptimal response to treatment are likely to have shown some improvement in their mood and psychosocial functioning, but the continued impairment and risk of relapse warrant further treatment. Following an initial trial of medication, the clinician is challenged with evaluating the remaining symptoms and selecting a treatment that will optimize the outcome, one that will hopefully target and improve the remaining depressive symptoms.

Individual Residual Symptoms During Partial Response

By virtue of the definition of partial response, it is expected that patients who partially respond to treatment will continue to show residual symptoms. As mentioned above, however, there has been little focus on which individual symptoms tend to persist following treatment. Paykel,[9] in a longitudinal study of 64 patients with major depression, found that over 75% of the patients with partial response (HAM-D score of 8–18) had mild or moderate residual general somatic symptoms and fatigue, psychic anxiety, somatic anxiety, genital symptoms, or depressed mood, while over half had insomnia or guilt. We are unaware of any other study that has elaborated on the specific symptoms leftover in partial responders. Thus, despite the fact that all patients who are partial responders continue to have symptoms, we have little information on which symptoms are most common and whether these residual symptoms tend to cluster into related symptomatic groups.

Residual Symptoms During Full Remission

Though it is not surprising that patients who partially respond to treatment report residual symptoms, Nierenberg et al.[2] found that of the patients who successfully or fully responded to antidepressant medication (HAM-D score ≤ 7), less than 20% report being symptom-free following treatment. The most common residual symptoms found were sleep disturbances (44%), fatigue (38%), and disinterest (27%). Patients who had these symptoms after treatment tended to have had them at baseline, that is, the symptoms were generally not treat-

ment emergent. Similarly, Fava et al.[1] found that of 49 patients in remission after 3 to 5 months of full doses of antidepressant medications, only 6 patients reported no residual symptoms following treatment. Of the remaining patients, 73% reported generalized anxiety, 55% reported somatic anxiety, and 40% reported irritability.

These data suggest that even though patients may respond to treatment and a full diagnosis of the mood disorder is no longer appropriate, many patients continue to experience residual symptoms. Considering the importance of the effect of residual symptoms on relapse, recurrence, and other long-term outcomes reviewed below, these symptoms should not be overlooked.

IMPORTANCE OF RESIDUAL SYMPTOMS

Contribution to Relapse

Patients who report residual symptoms have a higher risk of relapse than patients who do not report residual symptoms.[9,25–29] In the National Institute of Mental Health (NIMH) Collaborative Depression Program, naturalistic follow-up showed that, after recovery from major depressive disorder, patients with residual subsyndromal depression had an odds ratio of 3.5 for subsequent relapse compared with those who had a full acute recovery.[6]

In a 1-year follow-up study of 101 patients,[27] relapsers were shown to have had higher levels of residual symptoms at the time of remission. Residual symptoms also predicted relapse during drug continuation in a study of the elderly and in 2 drug-discontinuation controlled trials.[28,29] Paykel et al.[26] found that 76% of patients with residual symptoms relapsed within 10 months of treatment, whereas 25% of patients without residual symptoms relapsed within the same time period. Thase et al.[7] found that, among patients who responded to treatment and maintained HAM-D scores of ≤ 10 for 2 consecutive weeks, 52% relapsed over the next year, while of those who maintained a HAM-D score of ≤ 6 for 2 consecutive months following treatment, only 9% relapsed over the next year.

There is, then, considerable agreement across studies that residual symptoms contribute to relapse vulnerability. Treatment of residual symptoms may, therefore, not only be important for reducing suffering but may also reduce the risk of future major depressive episodes.[30] Two studies have examined the effect of treating patients with residual symptoms on relapse rates over the next 1 to 4 years. Both studies found a reduction in residual symptoms with the addition of cognitive-behavioral therapy (CBT) to the medication regimen that had yielded the partial response. Fava et al.[1] reported a difference in relapse rates at 4 years between continued medication (70% relapse rate) and augmentation with CBT (35% relapse rates). Paykel et al.[30] found that the addition of CBT to medication reduced relapse rates at 68 weeks from 47% for medication alone to 29% with CBT. Thus, it appears that reducing residual symptoms may affect the important long-term outcome of relapse.

Contribution to Disability

Severity of depressive symptomatology is related to occupational[8] and psychosocial[10] impairment. Occupational functioning is regularly worse for patients who continue to report symptoms following treatment compared with those who experience symptom relief.[8] Judd et al.[5,25] found, in a 12-year prospective study, that subsyndromal symptoms persisting after the resolution of a depression are also associated with a variety of poor outcomes, including greater health care utilization (medical, psychiatric, and emergency care), more psychiatric hospitalizations, more public assistance (welfare/disability benefits), and more suicidal thoughts and behaviors.

This group also found, however, that the psychosocial disability is state dependent; when the symptoms are present, even if they are mild or subthreshold, the disability exists, but when the patients are asymptomatic, the disability decreases and overall psychosocial functioning improves.[10] Residual symptoms that are rated mild or subthreshold are related to a slight, but significant, increase in impaired psychosocial functioning compared with remission with no residual symptoms, having a greater impact on occupational functioning than interpersonal functioning.[10]

Consistent with these results, Mintz et al.,[8] in a meta-analysis of 10 clinical trials, describe a near-linear relationship between residual symptoms and the probability of functional and affective work impairment. The model they applied to their analysis suggested that even mild residual symptoms would result in impairment. These findings reinforce the importance, for the long-term outcome of disability, of treating even relatively mild residual symptoms.

CAN RESIDUAL SYMPTOMS BE EFFECTIVELY TREATED?

Fatigue

Until recently, there has been little study of the problem of fatigue in patients with a primary diagnosis of depression. This is especially true of fatigue as a residual symptom. Despite the lack of attention that fatigue has received, it appears to be an important variable in depression. Between 73% and 96% of depressed patients, depending on the methodology of the study, have significant fatigue at baseline,[31–33] and Moos and Cronkite[31] found that fatigue was the most potent predictor of progressing to a chronic course in 313 unipolar patients treated over a 10-year period. Fatigue also appears to be a common residual

symptom in treated depression. Fava et al.[1] reported, for instance, that 10% of patients with successfully treated major depression continued to complain of fatigue, and Nierenberg et al.[2] found that 35% of patients with remitted depressions continued to complain of fatigue. While much of residual fatigue may be a core depressive symptom, it can also be related to the use of antidepressants.[34]

Treatment of fatigue, in the context of depression, has not been studied to any great extent. Amphetamines were, at one time, widely used to treat depressive states and fatigue, but their use declined dramatically with the introduction of effective antidepressants and the increasing awareness of the abuse potential associated with stimulants.[35] Both methylphenidate and pemoline have been reported to be of use in improving alertness and in treating fatigue and depression in small controlled trials that lack the rigor of modern trial methodology.[36,37] There are also a number of more recent open-label trials of stimulants in medically ill patients that report improvement in depression, though the effect on fatigue or energy is generally not systematically reported.[38]

A recently released novel stimulant, modafinil, has begun to receive some attention in the treatment of fatigue and sleepiness in depressed patients. Modafinil appears to have a number of advantages over the classical stimulants, including ease of use, lack of abuse potential, and a favorable tolerability profile. One retrospective case series[39] and 1 open-label study[40] using modafinil have suggested that this compound might be of use for fatigue in patients with depression. While these initial results appear promising, controlled trials will be necessary to define the role of modafinil as a treatment for fatigue in depressed patients.

Other authors have attempted to evaluate, in the context of depression, the effects of antidepressants on fatigue. For instance, Judge et al.[41] analyzed data from 7 clinical trials involving 2075 patients with major depression using the HAM-D retardation factor score (total of items 1, 7, 8, and 14) as the primary measure of energy improvement. While this subscale of the HAM-D may be a poor measure of fatigue, their findings demonstrate that patients experience an improvement in depressed mood, libido, psychomotor retardation, and work and interests from baseline to endpoint when treated with fluoxetine.

Despite the widespread practice of using "stimulating" antidepressants such as bupropion and venlafaxine, as well as medications such as thyroid hormone, for fatigue in depressed patients, there are few published data on their use for this indication. There are 3 case reports suggesting that bupropion may be useful for selective serotonin reuptake inhibitor (SSRI)–induced fatigue,[42] and 1 case of the successful use of venlafaxine in chronic fatigue associated with depression.[43] Thyroid hormone, which increases energy in patients with hypothyroidism, has been studied as an augmenting agent in depression.[44] Despite its intuitive appeal in depressed patients with fatigue, the augmentation studies do not detail its effect on fatigue.

Because fatigue is both common and potentially treatable in patients with depression, it is a prime target for research. Evaluation of the treatment of residual fatigue would help to define its role in quality of life, relapse, and disability.

Sexual Dysfunction

The relationship of depression, antidepressant treatment, and sexual dysfunction is dynamic and complex. The background prevalence of sexual dysfunction in the general population is high. A recent U.S. study found that 43% of women and 31% of men experience some type of sexual dysfunction.[45] The figures seem to be still higher in patients with depression. In patients with nonpsychotic major depression without concurrent medical illness, over 40% of men and 50% of women reported decreased sexual interest.[46] Sexual symptoms are also a significant component of residual depression. A study of treated patients in partial remission found that 53% showed moderate-to-severe sexual symptoms and 26% showed mild sexual symptoms.[9] Sexual dysfunction may also be a side effect of antidepressants.[47] A recent large prospective study reports an incidence of adverse sexual effects from antidepressants of more than 50%.[48] Other studies suggest that most patients report improvement in overall sexual functioning from the time they start antidepressants until follow-up.[49] Presumably, as depression improves, so does overall sexual functioning.

Sexual symptoms, both treatment emergent and residual, are not only common, but they also have obvious practical implications, as the negative consequences of the symptoms can reinforce the depression. In other words, there may be a direct relationship between experiencing sexual symptoms and depression. This point was illustrated in a recent study by Seidman et al.,[50] in which 152 men with erectile dysfunction and depression were treated with sildenafil or placebo. Effective treatment of erectile dysfunction (without an antidepressant) resulted in significant improvement in both depression and quality of life, which raises the possibility that treatment of residual erectile dysfunction in depressed patients may have wide-ranging effects on depression and related outcomes such as quality of life.

With the introduction of the phosphodiesterase inhibitor sildenafil, an efficacious treatment for some depressed patients with sexual dysfunction is available. Sildenafil has been reported to be of use in men with antidepressant-related erectile dysfunction and in women with antidepressant-related anorgasmia.[51,52] In addition, bupropion and mirtazapine may also have the potential to

reverse the adverse effects of other antidepressants and perhaps to improve some forms of sexual dysfunction.[53–59]

We should now be able to begin investigating the importance and treatment of sexual dysfunction in depression, whether it is treatment emergent or residual. The clarification of these issues may widen the options available to the clinician as well as lead to improved long-term outcomes in patients with depression.

Anxiety

Major depression is accompanied by significant anxiety in up to 62% of patients,[60,61] and the presence of anxiety seems to predispose to, accelerate, worsen, and lengthen the course of depression.[62–66] In addition, the presence of anxiety is associated with a poorer response to antidepressants.[67,68] In the Depression Research in European Society II survey, patients with severe depression associated with anxiety had significantly higher functional disability than other depressed patients without anxiety.[69] Anxiety is also a common residual symptom in depression. In patients with major depression in partial remission, Paykel et al.[26] report moderate psychic anxiety in 42% and panic attacks, phobic anxiety, and somatic anxiety in 11% each.

While there are few published data on treating anxiety as a residual symptom in depressed patients, Fava et al.[1] did report that CBT was useful for residual symptoms, among which were anxiety symptoms. In general, therapeutic approaches to comorbid depression and anxiety include both pharmacologic and psychotherapeutic options, and a number of studies have examined response to medications in patients with depression and comorbid anxiety at baseline.[70] Benzodiazepines appear to be quite effective in short-term treatment,[71] but questions about their long-term efficacy and safety have been raised. Though anxiety is not directly discussed, clonazepam has been found useful as augmentation in prolonged depression with suboptimal improvement.[72]

Atypical antipsychotics, including both risperidone and olanzapine, have recently been shown to be useful for augmentation in treatment-resistant depression.[73,74] While these drugs may also be of use in some anxiety states,[75,76] it is not clear if their use in treatment-resistant depression is mediated by anxiolysis. Furthermore, whether they would be useful in partial responders with residual anxiety is not clear. Another interesting option is the use of buspirone, an antianxiety agent that has intrinsic antidepressant properties and has been used as an augmentation agent in the treatment of refractory depression.[77] Again, whether this medication would be useful in partial responders with residual anxiety is not clear. A variety of other medications that are useful in anxiety states, including β-blockers, SSRIs, and possibly antiepileptics such as gabapentin, may be of interest in the model of symptomatic treatment of residual anxiety symptoms.

Considering the comorbidity rates of depression and anxiety, as well as the treatment options available, the presence of anxiety as a residual symptom is of particular concern and in need of specific attention.

Sleep Disturbance

Sleep disturbances, which may affect one third of the adult population,[78] have an intimate and complex relationship with depression. In the general adult population, 14% to 20% of subjects complaining of insomnia showed evidence of major depression compared with less than 1% in those without sleep complaints.[79] Sleep disturbances are associated with an increased risk of subsequent depression. In the NIMH/Epidemiologic Catchment Area study, individuals with insomnia or hypersomnia persisting at 2 interviews 1 year apart were at higher risk of developing new major depression (adjusted odds ratio = 39.8 for insomnia and 46.9 for hypersomnia).[79] Persistent sleep disturbance is also associated with a chronic illness course, lower quality of life,[80] increased health care resource utilization,[81] and increased risk of both relapse and recurrence,[79,82] as well as increased suicide risk.[83] A significant number of patients showing partial response to antidepressant treatment continue to have sleep disturbances, with Paykel[9] reporting early insomnia in 48%, middle insomnia in 53%, and late insomnia in 16% of these patients. Nierenberg et al.[2] reported that 44% of patients who met criteria for remission continued to complain of sleep disturbances. They also reported that nearly all of the patients who had residual sleep disturbances had the problem at the beginning of treatment and that the symptoms were not, therefore, treatment emergent.

Despite the clear relationship of depression and sleep difficulties, any assessment of residual sleep problems in depressed patients needs to include a review of treatment-emergent sleep problems, as many antidepressants do interfere with sleep.[84] Furthermore, primary sleep disorders such as obstructive sleep apnea are commonly comorbid with depression and need to be addressed independently.

It is common clinical practice to use an adjunctive sleep medication in depressed patients, and the 1 available controlled trial supports the usefulness of this strategy. Asnis et al.[85] reported on a 4-week, randomized, placebo-controlled trial of zolpidem in 190 depressed patients who had partial response (HAM-D score = 8) on treatment with SSRIs. Zolpidem was associated with significant improvements in sleep, sleep quality, and awakenings. Their report did not discuss changes in quality of life. A number of treatments, including zolpidem, trazodone, zaleplon, and CBT, could be used for residual sleep problems, each of which could plausibly improve long-term outcomes, such as relapse and quality of life.

DISCUSSION

Most patients continue to experience symptoms after treatment for depression, and these residual symptoms are associated with an increased risk of relapse as well as functional impairments. While the data are relatively sparse, we have attempted to illustrate that individual residual symptoms such as fatigue, sleep disturbance, sexual dysfunction, and anxiety not only continue to exist following treatment of depression, but may be quite typical. Some data have begun to emerge suggesting that these residual symptoms are treatable, but strategies to treat specific residual symptoms of depression have not been adequately researched.

For the clinician, the first step is to evaluate the residual symptom to try to determine if it is part of the depression, a side effect of treatment, or an independent comorbidity. If the residual symptom is not due to an independent comorbidity, a symptomatic approach may be helpful. There is some evidence that zolpidem, in the short term, may be of use for sleep difficulties, but trazodone, zaleplon, and quetiapine, among others, could also prove to be useful. For some forms of sexual dysfunction, sildenafil, bupropion, and mirtazapine may be of use. For fatigue, modafinil, psychostimulants, bupropion, and venlafaxine have all shown some degree of promise. For anxiety, buspirone, the benzodiazepines, and possibly the atypical antipsychotics appear to deserve further attention. There are currently no data indicating whether dose escalation, switching antidepressants, augmentation directed at the syndromic depression in general, or a symptom-based approach is the most useful in any individual patient.

Other residual symptoms, such as lack of initiative and motivation, difficulties with concentration and memory, and anhedonia, are also potential targets for this approach, though there are no data to support specific treatments for these problems.

While it is not the primary purpose of this article to discuss a theoretical heuristic for the relationship of symptoms and syndrome, a symptomatic approach to residual symptoms raises a variety of difficult conceptual/theoretical issues. Depression is a syndromic diagnosis, composed of a group of symptoms that were determined through empirical research. We are currently unable, to a large degree, to tease out the relationships between the syndrome and the symptoms. With all of the symptoms discussed in this article, one could posit a complex, potentially bi-directional relationship, and it is entirely possible that individual symptoms, in individual patients, may represent a complex overlay of etiologies. A symptom may be an integral part of depression, it may be an unrelated comorbidity, or it may be a side effect of treatment. Furthermore, a residual symptom may be implicated in prolonging or worsening the depression.

Devising treatments to specifically focus on residual symptoms raises many questions for further research. First, it will be necessary to determine if targeting specific residual symptoms actually leads to better long-term outcomes. Improved relapse rates, increased duration of remission, and improved quality of life are among the outcomes that may benefit. Similarly, does the depression as a whole improve as specific symptoms related to the depression improve? For example, it has been reported[50] that treating sexual dysfunction in depressed men leads to improvement in depression and quality of life. Would treatment of other symptoms such as fatigue and sleep difficulties have similar outcomes? A related question is whether treating the primary residual symptom leads to improvements in other symptoms as well. (For example, does targeting fatigue as a residual symptom also lead to improvements in interest and motivation?)

As mentioned earlier, it is also unclear as to when residual symptoms are sufficiently mild enough to exert no practical impact in important outcomes such as quality of life. At some point, it may be unreasonable or infeasible to attempt to make patients completely asymptomatic. The issue remains to be elucidated, as it may be that in depression it is possible and desirable to struggle for a completely or a nearly asymptomatic state.

An obvious long-term research goal is to determine whether a symptomatic approach is any better than a syndromic approach. That is, are we better off targeting residual symptoms, or just treating the symptoms as a partially treated depression and raising the dose of the current antidepressant, augmenting, or switching without regard to the residual symptomatic pattern? In general, the initial symptomatic profile of a patient is not predictive of response to a particular antidepressant,[86] supporting a syndromic approach to the selection of an antidepressant for initial treatment. However, our review of the available data on the treatment of residual symptoms suggests that the treatment of residual symptoms may be a different situation. Only controlled trials can answer this question.

Finally, further research should investigate the clustering of residual symptoms. For example, do fatigue, disinterest, and lack of motivation tend to present together, while anxiety, sleep disturbance, and appetite suppression tend to present together? If so, should treatment strategies for these clusters of symptoms differ from treatment strategies for overall depression?

Developing symptom-specific treatment strategies for patients suffering from residual symptoms of depression may be one step further in the pursuit of optimal treatment for depression.

Drug names: buspirone (BuSpar and others), bupropion (Wellbutrin and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), gabapentin (Neurontin), methylphenidate (Ritalin, Metadate, and others), mirtazapine (Remeron), modafinil (Provigil), olanzapine (Zyprexa), pemoline (Cylert and others), quetiapine (Seroquel), risperidone (Risperdal), sildenafil (Viagra), trazodone (Desyrel and others),

venlafaxine (Effexor), zaleplon (Sonata), zolpidem (Ambien).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, buspirone, clonazepam, olanzapine, and risperidone are not approved by the U.S. Food and Drug Administration for the augmentation treatment of depression; bupropion, fluoxetine, methylphenidate, modafinil, pemoline, and venlafaxine are not approved for the treatment of fatigue; gabapentin is not approved for the treatment of anxiety; bupropion and mirtazapine are not approved for the treatment of sexual dysfunction; quetiapine is not approved for the treatment of sleep disorders; sildenafil is not approved for the treatment of depression-related sexual dysfunction; and trazodone, zaleplon, and zolpidem are not approved for the treatment of sleep disorders in depressed patients.

REFERENCES

1. Fava GA, Grandi S, Zielezny M, et al. Cognitive-behavioral treatment of residual symptoms in primary major depressive disorder. Am J Psychiatry 1994;151:1295–1299
2. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. J Clin Psychiatry 1999;60:221–225
3. Fawcett J. Antidepressants: partial response in chronic depression. Br J Psychiatry 1994;165:37–41
4. Cornwall P, Scott J. Partial remission in depressive disorders. Acta Psychiatr Scand 1997;95:265–271
5. Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry 1998;55:694–700
6. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;50:97–108
7. Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatments. Am J Psychiatry 1992;149:1046–1052
8. Mintz J, Mintz LI, Arruda MJ, et al. Treatment of depression and the functional capacity to work. Arch Gen Psychiatry 1992;49:761–768
9. Paykel ES. Remission and residual symptomatology in major depression. Psychopathology 1998;31:5–14
10. Judd LL, Akiskal HS, Zeller PJ, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. Arch Gen Psychiatry 2000;57:375–380
11. Fava M. Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 18):4–11
12. Thase ME, Howland RH, Friedman ES. Treating antidepressant nonresponders with augmentation strategies: an overview. J Clin Psychiatry 1998;59(suppl 5):5–12
13. Fava GA, Kellner R, Munari F, et al. The Hamilton Depression Rating Scale in normals and depressives: a cross cultural validation. Acta Psychiatr Scand 1982;66:26–32
14. Montgomery S, Dufour H, Brion S, et al. The prophylactic efficacy of fluoxetine in unipolar depression. Br J Psychiatry Suppl 1988;3:69–76
15. Shea MT, Elkin I, Imber SD, et al. Course of depressive symptoms over follow-up: findings from the NIMH Treatment of Depression Collaborative Research Program. Arch Gen Psychiatry 1992;49:782–787
16. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: a 5-year prospective follow-up of 431 subjects. Arch Gen Psychiatry 1992;49:809–816
17. Reynolds CF, Frank E, Perel JM, et al. Combined pharmacotherapy and psychotherapy in the acute and continuation treatment of elderly patients with recurrent major depression: a preliminary report. Am J Psychiatry 1992;149:1687–1692
18. Taylor S, McLean P. Outcome profiles in the treatment of unipolar depression. Behav Res Ther 1993;31:325–330
19. Salomon DA, Keller MB, Leon AC, et al. Recovery major depression: a 10-year prospective follow-up across multiple episodes. Arch Gen Psychiatry 1997;54:1001–1006
20. Mojtabai R. Residual symptoms and impairment in major depression in the community. Am J Psychiatry 2001;158:1645–1651
21. Frank E, Kupfer D, Perel J, et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47: 1093–1099
22. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definition of terms in major depressive disorder. Arch Gen Psychiatry 1991;48:851–855
23. Prien RF, Carpenter LL, Kupfer DJ. The definition and operational criteria for treatment outcome of major depressive disorder. Arch Gen Psychiatry 1991;48:796–800
24. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response and other relevant outcomes: a focus on treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):5–9
25. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. J Affect Disord 1997;45:5–18
26. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25:1171–1180
27. Faravelli C, Ambonetti A, Planti S, et al. Depressive relapses and incomplete recovery from index episode. Am J Psychiatry 1986;49:888–891
28. Mindham RH, Howland C, Sheperd M. An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. Psychol Med 1973;3:5–17
29. Prien RF, Kupfer DJ. Continuous drug therapy for major depressive episodes: how long should it be maintained? Am J Psychiatry 1986;143: 18–23
30. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. Arch Gen Psychiatry 1999;56:829–835
31. Moos RH, Cronkite RC. Symptom-based predictors of a 10-year chronic course of treated depression. J Nerv Ment Dis 1999;187:360–368
32. Tylee A, Gastpar M, Lepine JP, et al, for the DEPRES Steering Committee. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. Int Clin Psychopharmacol 1999;14:139–151
33. Baker M, Dorzab J, Winokur G, et al. Depressive disease: classification and clinical characteristics. Compr Psychiatry 1971;12:354–365
34. Hallerstein DJ, Yanowitch P, Rosenthal J, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. Am J Psychiatry 1993;150:1169–1175
35. Chiarello RJ, Cole JO. The use of psychostimulants in general psychiatry. Arch Gen Psychiatry 1987;44:286–295
36. Robin AA, Wiseberg S. A controlled trial of methylphenidate (Ritalin) in the treatment of depressive states. J Neurol Neurosurg Psychiatry 1958; 21:55–57
37. Elizur A, Wintner I, Davidson S. The clinical and psychological effects of pemoline in depressed patients: a controlled study. Int Pharmacopsychiatry 1979;14:127–134
38. Masand PS, Tesar GE. Use of stimulants in the medically ill. Psychiatr Clin North Am 1996;19:515–547
39. Menza MA, Kaufman K, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry 2000;61:378–381
40. DeBatista C, Solvason HB, Flores BH, et al. Modafinil as an adjunctive agent in the treatment of fatigue and hypersomnia associated with depression. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
41. Judge R, Plewes JM, Kumar V, et al. Changes in energy during treatment of depression: an analysis of fluoxetine in double-blind, placebo-controlled trials. J Clin Psychopharmacol 2000;20:666–672
42. Green TR. Bupropion for SSRI-induced fatigue [letter]. J Clin Psychiatry 1997;59:174
43. Goodnick PJ. Treatment of chronic fatigue with venlafaxine [letter]. Am J Psychiatry 1996;153:294
44. Joffe RT. Refractory depression: treatment strategies, with particular reference to the thyroid axis. J Psychiatry Neurosci 1997;22:327–331
45. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999;281:537–544
46. Kennedy SH, Dickens SE, Eisfeld BS, et al. Sexual dysfunction before antidepressant therapy in major depression. J Affect Disord 1999;56: 201–208
47. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999;19:67–85
48. Montejo AL, Llorca G, Izquierdo JA, et al, for the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Incidence of

sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. J Clin Psychiatry 2001;62(suppl 3):10–21
49. Michelson D, Schmidt M, Lee J, et al. Changes in sexual function during acute and six-month fluoxetine therapy: a prospective assessment. J Sex Marital Ther 2001;27:289–302
50. Seidman SN, Roose SP, Menza M, et al. Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. Am J Psychiatry 2001;158:1623–1630
51. Nurnberg H, Lauriello J, Hensley P, et al. Sildenafil for sexual dysfunction in women taking antidepressants [letter]. Am J Psychiatry 1999;156:1664
52. Nurnberg HG, Gelenberg A, Hargreave TB, et al. Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Am J Psychiatry 2001;158:1926–1928
53. Modell JG, Katholi CR, Modell JD, et al. Comparative sexual side effects of bupropion, fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther 1997;61:476–487
54. Segraves RT, Croft H, Kavoussi R, et al. Bupropion sustained release (SR) for the treatment of hypoactive sexual desire disorder (HSDD) in nondepressed women. J Sex Marital Ther 2001;27:303–316
55. Modell JG, May RS, Katholi CR. Effect of bupropion SR on orgasmic dysfunction in nondepressed subjects: a pilot study. J Sex Marital Ther 2000;26:231–240
56. Rowland DL, Myers L, Culver A, et al. Bupropion and sexual function: a placebo-controlled prospective study on diabetic men with erectile dysfunction. J Clin Psychopharmacol 1997;17:350–357
57. Boyarsky BK, Haque W, Rouleau MR, et al. Sexual functioning in depressed outpatients taking mirtazapine. Depress Anxiety 1999;9:175–179
58. Labbate LA, Grimes JB, Hines A, et al. Bupropion treatment of serotonin reuptake antidepressant-associated sexual dysfunction. Ann Clin Psychiatry 1997;9:241–245
59. Hirschfeld RMA. Care of the sexually active depressed patient. J Clin Psychiatry 1999;60(suppl 17):32–35
60. Fawcett J, Kravitz HM. Anxiety syndromes and their relationship to depressive illness. J Clin Psychiatry 1983;44(8 pt 2):8–11
61. Kessler RC, Nelson CB, McGonagle KA, et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US national comorbidity survey. Br J Psychiatry 1996;168(suppl 30):17–30
62. Parker G, Wilhelm K, Asghari A. Early onset depression: the relevance of anxiety. Soc Psychiatry Psychiatr Epidemiol 1997;32:30–37
63. Fava M, Rankin MA, Wright EC, et al. Anxiety disorders in major depression. Compr Psychiatry 2000;41:97–102
64. Ballenger JC. Comorbidity of panic and depression: implications for clinical management. Int Clin Psychopharmacol 1998;13(suppl 4): S13–S17
65. Grunhaus L, Rabin D, Greden JF. Simultaneous panic and depressive disorders: response to antidepressant treatment. J Clin Psychiatry 1986;47:4–7
66. Gaynes BN, Magruder KM, Burns BJ, et al. Does a coexisting anxiety disorder predict persistence of depressive illness in primary care patients with major depression? Gen Hosp Psychiatry 1999;21:158–167
67. Lydiard RB, Brawman-Mintzer O. Anxious depression. J Clin Psychiatry 1998;59(suppl 18):10–17
68. Lydiard RB. Coexisting depression and anxiety: special diagnostic and treatment issues. J Clin Psychiatry 1991;52(suppl 6):48–54
69. Tylee A, Gaspar M, Lepine JP, et al. Identification of depressed patient types in the community and their treatment needs: finding from the DEPRES II (Depression Research in European Society II) survey. Int Clin Psychopharmacol 1999;14:153–165
70. Rapaport MH. Prevalence, recognition, and treatment of comorbid depression and anxiety. J Clin Psychiatry 2001;62(suppl 24):6–10
71. Laws D, Ashford JJ, Anstee JA. A multicentre double-blind comparative trial of fluvoxamine versus lorazepam in mixed anxiety and depression treated in general practice. Acta Psychiatr Scand 1990;81:185–189
72. Morishita S, Aoki S. Clonazepam in the treatment of prolonged depression. J Affect Disord 1999;53:275–278
73. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry 1999;60: 256–259
74. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001; 158:131–134
75. Wilner KD, Anziano RJ, Johnson AC, et al. The anxiolytic effect of the novel antipsychotic ziprasidone compared with diazepam in subjects anxious before dental surgery. J Clin Psychopharmacol 2002;22:206–210
76. Tollefson GD, Sanger TM, Beasley CM, et al. A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998;43:803–810
77. Appelberg BG, Syvalahti EK, Koskinen TE, et al. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry 2001;62:448–452
78. Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411–418
79. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989; 262:1479–1484
80. Hatoum HT, Kong SX, Kania CM, et al. Insomnia, health-related quality of life and health care resource consumption: a study of managed care organization enrollees. Pharmacoeconomics 1998;14:629–637
81. Weyerer S, Dilling H. Prevalence and treatment of insomnia in the community: results from the Upper Bavarian Field Study. Sleep 1991; 14:392–398
82. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990;147:1189–1194
83. Wingard DL, Berkman LF. Mortality risk associated with sleeping patterns among adults. Sleep 1983;6:102–107
84. Thase ME. Depression, sleep, and antidepressants. J Clin Psychiatry 1998;59(suppl 4):55–65
85. Asnis GM, Chakraburtty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. J Clin Psychiatry 1999; 60:668–676
86. Rush JA, Batey SR, Donahue RMJ, et al. Does pretreatment anxiety predict response to either bupropion SR or sertraline? J Affect Disord 2001;64:81–87

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